APPENDIX A. SEARCH STRATEGIES

ANTIPLATELET THERAPY – SEARCH METHODOLOGY

Database Searched and Time Period Covered:
PubMed – From inception to 12/17/2015

Language:
English

Search Strategy:
"Platelet Aggregation Inhibitors"[Mesh] OR antiplatelet therap* OR anti-platelet therap*
AND
pci OR percutaneous coronary intervention*
NOT
stop OR stopped OR stopping OR discontinu*

Database Searched and Time Period Covered:
PubMed – From inception to 12/17/2015

Language:
English

Search Strategy:
“Similar Article” searches on the following articles:


Databases Searched and Time Period Covered:
Web of Science and Scopus – From inception to 12/17/2015

Language:
English

Search Strategy:
“Forward (Citation)” searches on the 3 articles cited above.
## APPENDIX B. PEER REVIEW COMMENTS/AUTHOR RESPONSES

<table>
<thead>
<tr>
<th>Comments</th>
<th>Response</th>
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</thead>
<tbody>
<tr>
<td>p 6; line 15: typo - these</td>
<td>This has been corrected.</td>
</tr>
<tr>
<td>p 7; line 13; dual antiplatelet therapy might be better defined as &quot;(aspirin plus a P2Y12 inhibitor)&quot; rather than (almost always clopidogrel and aspirin). Historically, clopidogrel and aspirin has been prescribed. But, use of newer agents such as ticagrelor (and prasugrel) are increasing.</td>
<td>This has now been corrected to &quot;aspirin plus a P2Y12 inhibitor.&quot; We also elected to add your additional clarification. &quot;Historically, clopidogrel and aspirin has been prescribed. But, use of newer agents such as ticagrelor and prasugrel are increasing.&quot;</td>
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<td>p. 22; key question 4: I would suggest mentioning whether any of the newer antiplatelet agents were included (or state that only clopidogrel was studied). The differentiation is noteworthy because theoretically there may be a concern of more bleeding with ticagrelor/prasugrel since they are more potent antiplatelet agents than clopidogrel.</td>
<td>Yes, we included any of the P2Y12 agents, which we clarified on page 4, paragraph 3; and page 9, paragraph 1. &quot;We did not exclude studies based on the type of APT management (ie, all P2Y12 agents were eligible).” Of note, the majority of the included studies looked at clopidogrel.</td>
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</table>
| p. 24; Is the evidence strong enough to conclude that the heterogeneity observed suggests factors other than periop management of antiplatelet therapy are responsible for differences? Or, have no differences been detected because no clinical trials have been conducted adequately assessing for outcomes differences? Would "may" be a better description rather than "suggests"? It would also be helpful to provide some examples of other factors that may influence bleeding/MACE in this population and whether the examples are supported by evidence. | We agree with your comments and have changed the conclusions (page 6, last paragraph; and page 22, first paragraph). “This heterogeneity, combined with small sample sizes, limited the ability to assess the impact of the different aspects of APT – timing of cessation, bridging, restarting therapy, and type of APT. Additionally, the varied range of invasiveness of the procedure, skin excisions to major thoracic cases, contributes to the operative bleeding risk and MACE risk, yet many studies lacks sufficient detail to assess the impact of procedure on the outcomes. These results also suggest that clinical factors other than perioperative APT may be in part responsible for differences in bleeding and MACE rates observed between studies.” Similar edits were made for page 5, last paragraph. “The heterogeneity observed limited the ability to adequately assess the impact of APT management for the wide range of procedures. It is likely that factors other than perioperative management of APT play a role in differences in bleeding and MACE rates observed between studies.” We also provided to the discussion more comments about possible other reasons for developing MACE or bleeding events and added these sentences to our discussion (page 23, paragraph 2). “We theorize that several factors make work in conjunction and be associated with bleeding and MACE events, but the data were too limited to help address this. For example, it is likely that the type of APT and the invasiveness of the operation combined may be associated with bleeding and MACE. However, the majority of studies included a wide range of procedures (skin excision through to thoracic surgery) and the APT management also varied between studies (timing, dual versus single preoperative, cessation versus continuing, and use of bridging).
Additionally, the outcomes and APT management were often only reported for cases where an event occurred, thus the management of those without an event was unknown. This prevented us from identifying whether one APT management, for a particular type of procedure or group of procedures was protective or harmful. Another possibility is that whether or not the patients’ cardiac status was optimized or if they were satisfactorily cleared from a cardiac standpoint was absent from the studies. For example, we could not assess the adequacy of their level of beta blockade, functional status, or cardiac function at the time of surgery. Additionally, perioperative management can also impact development of MACE, such as fluid management, which was not reported in the studies.”

| Appendix C | We made some cosmetic edits to this appendix to help improve the presentation of the data. |
## APPENDIX C. EVIDENCE TABLES

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Sample Description</th>
<th>Setting</th>
<th>Surgical procedures</th>
<th>APT management</th>
<th>Outcomes Follow-up</th>
</tr>
</thead>
</table>
| Alshawabkeh et al, 2013\(^{13}\) | Sample size; 51, 86% elective, rest urgent Cardiac stent type: DES Mean age: 65 Percent female: 0 | One center Academic USA retrospective | Vascular, Abdominal, Orthopedic, Neuro, Endoscopy, Other | **Preoperative**: Dual: ASA/clopidogrel  
**APT prior to surgery**: Dual 100%  
**APT management at surgery**: Dual, clopidogrel held: 100%; all therapy held: 35%; ASA continued in 65%.  
**Antiplatelet cessation >5d, all held**: Yes  
**Management assessed for post-op outcomes**: Hold all antiplatelet therapies, Hold one  
**Bridging therapy**: Yes, clopidogrel was discontinued for 5 to 7 days prior to surgery. On the day following clopidogrel discontinuation, patients were admitted for glycoprotein IIa/IIb inhibitor (mean 7.1 days treatment). | **Outcomes measured**: MACE or other cardiac (MI, death, etc), Bleeding, Other, LOS  
**Follow-up**: Less than 30 day |
<table>
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</table>
| Marcos et al, 2011<sup>14</sup> | Sample size: 21 noncardiac (also 16 cardiac cases) Cardiac stent type: DES Mean age: 66, includes 41% CABG Percent female: 30.6 | One center Academic Netherlands retrospective | Abdominal, Orthopedic, Endoscopy, Other | **Preoperative:** Dual: clopidogrel/ASA  
**APT prior to surgery:** Dual 100%  
**APT management at surgery:** Dual, clopidogrel held: 100%; all therapy held: 7/36 (19.4%)  
**Antiplatelet cessation >5d, all held:** Yes, 19.4%  
**Management assessed for post-op outcomes:** Hold all antiplatelet therapies, Hold ASA  
**Bridging therapy:** Yes, clopidogrel was discontinued 5 days before, patients admitted 2 days in advance. Patients who discontinued clopidogrel /ASA were admitted 3 days before. Labs assayed 2 h before and 6 h after starting Tirofiban. Labs continued once a day with ECG twice a day. Tirofiban was interrupted 4 h before procedure. If no postoperative risk of bleeding, clopidogrel resumed 12-24 h. If high risk for bleeding, heparin IV until risk decreased. Postintervention monitoring by ECG every 2 h during recovery for complaints of chest pain | **Outcomes measured:** MACE or other cardiac (MI, death, etc), Bleeding  
**Follow-up:** 30 day |
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</table>
| Yamamoto et al, 2014  | Sample size: 151 Cardiac stent type: BMS and DES Mean age: 70.4 Percent female: 17.9 | One center Academic Japan retrospective | Vascular, Abdominal, Orthopedic, Neuro, Other | **Preoperative:** Single, ASA; Single, non-aspirin; Dual: clopidogrel/ASA  
**APT prior to surgery:** Dual: 63/151 (41.7%), Single: 68/151 (45%), Other: Single + Heparin 20/151 (13.2%)  
**APT management at surgery:** Dual, clopidogrel held; Single aspirin, continued; some bridge with heparin  
**Antiplatelet cessation >5d, all held:** Yes: clopidogrel 100% of patients  
**Management assessed for post-op outcomes:** Hold all antiplatelet therapies, Hold one (if on dual), Continue existing  
**Bridging therapy:** Yes, 20 received heparin | Outcomes measured: MACE or other cardiac (MI, death, etc), Bleeding  
Follow-up: Unclear |
| Tanaka et al, 2014    | Sample size: 111, 84% on dual therapy Cardiac stent type: DES Mean age: 71 Percent female: 13.5% | One center Academic Japan retrospective | Endoscopy, Other | **Preoperative:** Single, ASA; Single, non-aspirin; Dual: thienopyrdine/ASA  
**APT prior to surgery:** Dual: 83.8%; Single: ASA; Other: 8% on warfarin, 6% on cilostazol  
**APT management at surgery:** 100% all oral APT held  
**Antiplatelet cessation >5d, all held:** Yes: 100% (mean 7.0 days before procedure)  
**Management assessed for post-op outcomes:** Hold all antiplatelet therapies  
**Bridging therapy:** No | Outcomes measured: MACE or other cardiac (MI, death, etc)  
Follow-up: Greater than 30 day  
Less than 30 day |
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<tr>
<th>Author, year</th>
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<tbody>
<tr>
<td>Sonobe et al, 2011&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Sample size: 38 Cardiac stent type: BMS and DES Mean age: 71.3 Percent female: 13.2</td>
<td>One center Academic Japan retrospective</td>
<td>Other</td>
<td>Preoperative: Single, ASA; Dual ASA/clopidogrel and ASA/Ticlopidine; (and some on warfarin) APT prior to surgery: Dual: ASA/clopidogrel 21.1%, ASA/ticlopidine 21.1%; Single: ASA 55.3%; None: 2.6; also 23% were on warfarin (overlap with APT unknown). APT management at surgery: Dual, all therapy held: 42.2%; Single ASA, held: 55.3% Antiplatelet cessation &gt;5d, all held: Yes: Most 7 days, except 7.8% 3 days and 2.6% 5 days. Management assessed for post-op outcomes: Hold all antiplatelet therapies Bridging therapy: Yes, in some, 16/38 (42%) heparin, but 7 were already on warfarin.</td>
<td>Outcomes measured: MACE or other cardiac (MI, death, etc), Bleeding, Atrial fibrillation Follow-up: Less than 30 day; 30 day</td>
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<td>Cerfolio et al, 2010&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Sample size: 64 Stent subset. No mention of elective/urgent Cardiac stent type: BMS and DES Mean age: 67.2 Percent female: 24.9%</td>
<td>One center Academic USA prospective</td>
<td>Other</td>
<td>Preoperative: Single, aspirin; Dual, clopidogrel/ASA <strong>APT prior to surgery</strong>: Dual: 42% clopidogrel/ASA; Single: 58% clopidogrel; Other: 132 controls for propensity analysis not on clopidogrel, but most on ASA 32.6% of controls had cardiac stent <strong>APT management at surgery</strong>: Dual, all therapy continued: 14 patients; Single clopidogrel, continued: 19 patients <strong>Antiplatelet cessation &gt;5d, all held</strong>: No <strong>Management assessed for post-op outcomes</strong>: Continue existing <strong>Bridging therapy</strong>: No</td>
<td>Outcomes measured: MACE or other cardiac (MI, death, etc), Bleeding <strong>Follow-up</strong>: 30 day</td>
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<tr>
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| Ryan et al, 2013\(^1\) | Sample size: 85 Cardiac stent type: "cardiac stents" 12.9% of pts Mean age: 70 Percent female: 43% | One center, prospective, consecutive pts Academic Ireland prospective | Ophthalmology | **Preoperative:** Single, ASA; Single clopidogrel; Dual ASA/clopidogrel; Other: warfarin  
**APT prior to surgery:** Dual: 10.3% ASA/clopidogrel; Single: 72% ASA and 7.5% clopidogrel; Other: 10.3% warfarin  
**APT management at surgery:** All therapy continued, 100%. Dual, all therapy continued; Single ASA, continued; Single clopidogrel continued; Other: Warfarin continued  
**Antiplatelet cessation >5d, all held:** No  
**Management assessed for post-op outcomes:** Continue existing  
**Bridging therapy:** No | Outcomes measured: Bleeding  
Follow-up: 6 months |
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<tr>
<th>Author, year</th>
<th>Sample Description</th>
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<th>Surgical procedures</th>
<th>APT management</th>
<th>Outcomes Follow-up</th>
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| Capodanno et al, 2015²⁰ | Sample size: 515; 251 LMWH vs 264 no LMWH | Multiple centers Academic Italy retrospective | Vascular, Abdominal, Orthopedic, Neuro, Ophthalmology, Endoscopy, and other | **Preoperative:** Single, ASA; Dual clopidogrel/ASA  
**APT prior to surgery:** Dual: 31.5%; Single: 68.5%  
**APT management at surgery:** Patients categorized by antithrombotic regimen in the perioperative period. LMWH group discontinued antplatelet regimen (DAPT or ASA) and bridged with LMWH until antplatelet drugs were resumed. Clopidogrel/ASA discontinued at least 5 days and 48 hours before the procedure, respectively. No patients in LMWH group underwent procedure while on DAPT or ASA, without bridging.  
**Antiplatelet cessation >5d, all held:** Yes  
**Management assessed for post-op outcomes:** Bridging with LMWH vs no LMWH. See above.  
**Bridging therapy:** Yes, bridging with LMWH, but dosage and timing not described. | **Outcomes measured:** MACE or other cardiac (MI, death, etc), Bleeding MACE or other cardiac (MI, death, etc), Bleeding, Readmissions, Other, (stroke)  
**Follow-up:** 30 day |
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| Bolad et al, 2011<sup>21</sup> | Sample size: 220, 1770, 238 with noncardiac surgery (18BA; 79BMS; 141DES) Cardiac stent type: BMS and DES Mean age: 66 Percent female: 1.4 | One center Academic USA retrospective | Vascular, Abdominal, Orthopedic, Ophthalmology, Endoscopy | **Preoperative:** Single, ASA; Single, non-ASA; Dual  
**APT prior to surgery:** Dual: 10.4%; Single: 18.6% ASA only, 2% thienopyridine; None: 68.8%  
**APT management at surgery:** Dual, all therapy continued: 10.4%; Single ASA, continued: 18.6%; Single clopidogrel, continued: 2%; Other: 68.8% (weren’t on APT prior to surgery)  
**Antiplatelet cessation >5d, all held:** Not reported  
**Management assessed for post-op outcomes:** Hold all antiplatelet therapies  
**Bridging therapy:** No | **Outcomes measured:** MACE or other cardiac (MI, death, etc), Other: Stent Thrombosis  
**Follow-up:** 30 day |
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<tr>
<td>Hawn et al, 2013&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Sample size: 25,641; 28,029 patients had 41,989 procedures within 24 months of pci Cardiac stent type: BMS and DES Mean age: &gt; = 60 y/o (80.6%) Percent female: 1.6</td>
<td>Other, multisite VA data national retrospective cohort Academic USA retrospective</td>
<td>Vascular, Abdominal, Orthopedic, Neuro, Ophthalmology, other, Eye/ear, Resp, GU, Integ</td>
<td><strong>Preoperative:</strong> Single, ASA; Single, non-ASA; Dual <strong>APT prior to surgery:</strong> Dual (ASA/clopidogrel): 57.8%; Single 36.6%; None: 6.0% <strong>APT management at surgery:</strong> Dual, all therapy continued: 65.9%; Dual, clopidogrel held: 11.0%; Dual, ASA held: 4.3%; Dual, all therapy held: 18.9% Single ASA, continued: 82.7%; Single ASA, held: 17.3%; Single clopidogrel, continued: 66.7; Single clopidogrel, held: 33.3% <strong>Antiplatelet cessation &gt;5d, all held:</strong> Yes: 24.1% <strong>Management assessed for post-op outcomes:</strong> Hold one (if on dual) <strong>Bridging therapy:</strong> No</td>
<td><strong>Outcomes measured:</strong> MACE or other cardiac (MI, death, etc) <strong>Follow-up:</strong> 30 day <strong>Instruments used:</strong> none</td>
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<td>Assali et al, 2009</td>
<td>Sample size: 78 Cardiac stent type: DES Mean age: 65.7 Percent female: 20.5</td>
<td>One center Academic Israel retrospective</td>
<td>Vascular, Abdominal, Orthopedic, Neuro, Other</td>
<td>Preoperative: Dual APT prior to surgery: Unclear APT management at surgery: 10 (5.7%) no therapy, 51 (65.4%) on Single (ASA or clopidogrel), 17 (21.8%) on Dual Single ASA, continued: 18%; Single clopidogrel, continued: 42% Outcomes for ASA (with or without clopidogrel) and for clopidogrel (with or without ASA) Antiplatelet cessation &gt;5d, all held: 13% ASA and 24% clopidogrel Management assessed for post-op outcomes: Hold all antiplatelet therapies, Hold one (if on dual), Continue existing Bridging therapy: No</td>
<td>Outcomes measured: MACE or other cardiac (MI, death, etc), Bleeding MACE or other cardiac (MI, death, etc) Follow-up: Less than 30 day</td>
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| Brotman et al, 2007<sup>24</sup> | Sample size: 114 Cardiac stent type: DES Mean age: 71 Percent female: 34.3 | One center Academic USA retrospective | Vascular, Abdominal, Orthopedic, Neuro | Preoperative: Single, ASA; Single, non-ASA; Dual  
APT prior to surgery: Dual (ASA/clopidogrel): 77%  
APT management at surgery: Dual, all therapy continued: 21.1%, Single ASA, continued: 1.8%; Single clopidogrel, continued: 0%, Other: 77.2% no APT at time of surgery  
Antiplatelet cessation >5d, all held: Mean: 14d ASA; 14 Dual  
Yes: 77%  
Management assessed for post-op outcomes: Hold all antiplatelet therapies, Hold one (if on dual), Continue existing  
Bridging therapy: No | Outcomes measured: MACE or other cardiac (MI, death, etc), Bleeding  
Follow-up: 30 day |
| Choi et al, 2010<sup>25</sup> | Sample size: 27 Cardiac stent type: DES Mean age: 67.6 Percent female: 29.6 | One center Academic Korea prospective | Other | Preoperative: Dual  
APT prior to surgery: Dual: clopidogrel/ASA  
APT management at surgery: Dual, all therapy held: 100%  
Antiplatelet cessation >5d, all held: Yes, 100%: 4.96 +/- 0.71 days  
Management assessed for post-op outcomes: Hold all antiplatelet therapies  
Bridging therapy: No | Outcomes measured: MACE or other cardiac (MI, death, etc), Bleeding, Other: LOS  
MACE or other cardiac (MI, death, etc)  
Follow-up: Unclear |
<table>
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<tr>
<td>Conroy et al, 2007&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Sample size: 22, 42 procedures in 22 pts (incl 17 minor/surface procedures)</td>
<td>One center Academic Australia</td>
<td>Abdominal, Ortho, Endoscopy, Minor procedures</td>
<td>Preoperative: Single, Dual APT prior to surgery: 39/42 on dual (ASA/clopidogrel) APT management at surgery: 21/42 clopidogrel/ASA were continued; 3 cases clopidogrel had been stopped previously; 14 had clopidogrel stopped prior to surgery and ASA continued, 4 had clopidogrel stopped and underwent bridging. Antiplatelet cessation &gt;5d, all held: timing unknown Management assessed for post-op outcomes: Hold clopidogrel; bridging Bridging therapy: Yes, outpatient lovenox or inpatient tirofiban/heparin for 4 patients</td>
<td>Outcomes measured: MACE or bleeding Follow-up: Not described</td>
</tr>
</tbody>
</table>
APPENDIX D. CITATIONS FOR EXCLUDED STUDIES


11. Vlastarakos PV, Sampatakaki A, Kouloubinis A, Nikolopoulos TP. Perioperative maintenance of dual antiplatelet therapy is safe in patients requiring laser cordectomy for


82. Schouten O, van Domburg RT, Bax JJ et al Noncardiac surgery after coronary stenting: early surgery and interruption of antiplatelet therapy are associated with an increase in major
adverse cardiac events. Journal of the American College of Cardiology. Jan 2

83. Compton PA, Zankar AA, Adesanya AO, Banerjee S, Brilakis ES. Risk of noncardiac 
Nov 1 2006;98(9):1212-1213.

84. Reddy PR, Vaitkus PT. Risks of noncardiac surgery after coronary stenting. The American 

85. Sharma AK, Ajani AE, Hamwi SM et al Major noncardiac surgery following coronary 
stenting: when is it safe to operate? Catheterization and cardiovascular interventions : 
official journal of the Society for Cardiac Angiography & Interventions. Oct 
2004;63(2):141-145.

86. Brancati MF, Giammarinaro M, Burzotta F et al Outcome of non-cardiac surgery after stent 
implantation in the DES era: results of the Surgery After Stent (SAS) registry. The Journal 
of invasive cardiology. 2011;23(2):44-49.